Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 1-4, 6-9, 15-18 and 21-35 will be pending in the application, with claims 1, 21 and 32 being the independent claims. The pending claims read on the elected invention.

Claims 14, 19 and 20 are being cancelled without prejudice or disclaimer of the subject matter therein. Claims 1-4, 6-8, 15-18, 21-30 and 32-35 are being amended and claims 34-35 are being added. Support for the amendment and addition of claims may be found in the specification, for example, at paragraphs 0008 (p. 8), 0033-0034 (p. 10-11), 0044-0045 (p. 13) and 0059-0061 (p.17), and in the original claims. Accordingly, the amendments introduce no new matter.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

II. Rejection Under 35 U.S.C. § 112, First Paragraph: Enablement

The Examiner maintained the rejection of claims 1-4, 6-9, 14-18 and 20-27 under 35 U.S.C. § 112, first paragraph as allegedly being nonenabled for their full scope, and extended the rejection to new claims 28-33. (Office Action, pp. 2-3, ¶¶ 5-7.) The Examiner asserted that it would take undue experimentation to identify fusion intermediates for "all" claimed viruses. (*Id.*, p. 3, ¶ 7.) Applicants respectfully traverse the rejection.

In the previous reply, Applicants provided ample evidence in favor of the enablement of the full scope of the claimed invention, in the form of a review article discussing the highly advanced state of the art and the reasonable predictability of identifying fusion intermediates for a number of viruses. Eckert and Kim, *Annu. Rev. Biochem. 70*:777-810 (2001). Nevertheless, the Examiner stated that "[a]lthough some claimed viruses were suggested or hypothesized to share a common mechanism for inducing membrane fusion as HIV or influenza, the prior art has not demonstrated that this is the case." (Office Action, p. 3, ¶ 7.) Applicants submit that the Examiner has failed to provide *any* evidence whatsoever for not believing the evidence of record. Applicants submit that until the Examiner provides evidence to cast doubt upon the enablement of the present claims, the rejection should not be maintained. Nonetheless, Applicants provide below a more detailed discussion of the evidence in favor of enablement, for the Examiner's consideration.

A. Scope of the Claims

Applicants have amended independent claim 1 to recite a membrane bound viral envelope protein or membrane bound fragment thereof "from respiratory syncytial virus (RSV), parainfluenza virus type 3 (HPIV-3), human influenza viruses, measles virus or a retrovirus." In addition, claims 2 and 3 specify that the envelope protein or fragment thereof is from a retrovirus or HIV-1, respectively. Independent claim 21 recites gp120/gp41 or fragments thereof.

B. Guidance In the Specification

As discussed in the previous reply, the specification contains a detailed teaching of various fusion structures, including those of HIV-1, RSV, HPIV3 and measles virus. (Specification, pp. 20-45 and SEQ ID NOs:1-77), and teaches how to make antibodies against them. The specification would allow a person of ordinary skill in the art to make a multitude of antibodies that can be used in the practice of the claimed method without undue experimentation.

C. Guidance In the Prior Art

In addition, articles published before October 2002 taught methods of predicting additional fusion-related structures with sufficient accuracy to produce the recited antibodies. For example, Zhou et al. describe the prediction of two heptad repeat regions of human respiratory syncytial virus using the LearnCoil-VMF program that was mentioned in the Eckert and Kim review article. Zhou et al., *Proc. Nat'l Acad. Sci. USA 97*:14172-77 (2000). They synthesized a peptide corresponding to these predicted regions, joined by a linker region, and found that it forms a trimer in solution. *Id.* at 14174, col. 1 to 2. They treated the peptide with proteases to trim it to the smallest functional fragments. *Id.*, col. 2. They also verified the six-helix structure by crystallography. *Id.* at 14175. In addition, scientists had identified fusion-related structures from paramyxoviruses besides RSV. See, e.g., Joshi et al., *Virology 248*:20-34 (1998) and Baker et al., *Mol. Cell. 3*:309-19 (1999) (simian parainfluenze virus 5); McGinnes et al., *Virology 289*:343-52 (2001) (Newcastle disease virus). In addition, the fusion peptide of members of the paramyxovirus family is highly conserved, showing up to 90% identity. FIELDS VIROLOGY (4th Ed.), Knipe et al., eds., Lippincott Williams & Wilkins, Philadelphia (2001), p. 1320. Thus, the fusion peptide from any paramyxovirus could have been reasonably predicted.

Fusion structures for other viruses were also identified or predicted prior to October 2002. *See*, e.g., Chambers et al., *J. Gen. Virol. 71*:3075-80 (1990) (retroviruses, coronaviruses, influenza viruses, and paramyxoviruses); Poon and Chen, *J. Virol. 72*:1959-66 (1998) (HTLV-2) (*erratum* in *J. Virol. 72*:6278 (1998) (adding a citation)); Flint et al., *J. Virol. 73*:6782-90 (1999) (fusion peptide of HCV); Poumbourios et al., *IUBMB Life 48*:151-6 (1999) (Ebola virus); Rodriguez-Crespo et al., *Virology 15*:133-42 (1999) (fusion peptides of HBV, DHBV, and WHV); Berting et al., *Virus Res. 68*:35-49 (2000) (fusion peptide of HBV).

D. Conclusion

The state of the art concerning fusion-related structures was therefore extremely well-developed. The specification provides further guidance for such structures. Therefore, producing antibodies against fusion-related structures would not have required undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

VIII. Rejection Under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 1-4, 6-9, 14, 18 and 20-27 under 35 U.S.C. § 103 in view of U.S. 6,605,427 ("the '427 patent") in combination with Liang [sic, Jiang] (1998 and 1999) and extended the rejection to claims 26 [sic 28]-33. (Office Action, pp. 3-5, ¶¶ 8-13.) Applicants respectfully traverse the rejection.

A. The Present Claims Are Nonobvious Over the '427 Patent

Applicants submit that the present invention is nonobvious over the '427 patent. The cited patent describes a method of screening for compounds that selectively *inhibit* the induction of fusogenic structures or intermediates, and its screening method *requires the presence* of fusion inducers ("triggering agents"), such as cellular receptors and fragments thereof, to identify these inhibitory compounds. In the '427 patent, the screening assay is used to identify anti-viral compounds that work by "preventing or disrupting conformational changes in the viral transmembrane protein that are required for virus fusion." The '427 patent, e.g., abstract. The '427 patent only describes the identification of compounds that selectively "prevent," "disrupt," "inhibit," and "block" the formation of structures and intermediates that are required for fusion. *See* the '427 patent, throughout, e.g., col. 1, line 21; col. 4, line 66; col. 5, lines 5, 17-18, 28-29, 34-35 and 37; col. 7, line 17; and col. 10, lines 34, 40, 51 and 60-63.

The method described in the '427 patent comprises: (a) mixing (i) a viral envelope protein or glycoprotein, (ii) a triggering agent, and (iii) a candidate compound, and (b) measuring the effect of the candidate compound on the formation of conformational intermediates of viral fusion. *Id.*, claim 1, and col. 7, line 55 to col. 8, line 4. A triggering agent "interacts with the lipid bilayer/membrane-associated envelope protein or glycoprotein system *to induce entry-level structural or conformational changes* in the transmembrane or fusion protein of the viral envelope system." *Id.*, col. 9, lines 8-12 (emphasis added). Triggering agents include:

> a virus permissive cell, an insoluble or soluble receptor from said cell, or a functional fragment of said receptor. For purposes of the present invention, a "virus-permissive cell" is a cell into which a particular virus typically can enter and infect.

'The '427 patent, col. 9, lines 14-18. Moreover, "[r]eagent ii in the methods described above serves as a triggering agent" and "the screening method requires a triggering agent." *Id.*, col. 9, lines 12-13 and 7-8. Therefore, the method in the '427 patent *requires* the use of a *cellular* *receptor or fragment thereof* that induces a fusogenic structure or intermediate to test a candidate compound for the ability to inhibit the induction of fusion.

In contrast, the claimed invention is a method of screening for compounds that selectively *induce* conformational changes in viral envelope proteins *in the absence* of cellular receptors and fragments. As defined in the specification:

> The phrase "induce conformational changes" as employed herein is the induction of structures and conformational intermediates necessary for viral fusion and entry into permissive cells.

Specification, p. 17, ¶ 0061. The '427 patent does not teach or suggest screening for compounds that selectively *induce* fusogenic structures or intermediates. Nor does it teach or suggest carrying out the screening method in the absence of a cellular receptor or fragment thereof. In fact, the '427 patent teaches that a triggering agent such as a cellular receptor or fragment thereof is *required.*

Moreover, if the screening method of the '427 patent was carried out in the absence of a cellular receptor or fragment thereof, it could not be used to identify compounds that inhibit the formation of fusion structures or intermediates. Thus, modifying the method of the '427 patent as suggested by the Examiner would render it unsuitable for its intended purpose. However, "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP § 2143.01(V) (citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). In addition, to modify the '427 patent as suggested by the Examiner would change its principle of operation. *See In re Ratti*, 270 F.2d 810, 123 USPQ

349 (CCPA 1959); *see* also MPEP § 2143.02(VI). Therefore, claims 1, 21 and 32, and their dependent claims, are nonobvious over the '427 patent.

Claims 4 and 6 are additionally nonobvious over the '427 patent because they require a different detection step than that of '427 patent. The '427 patent teaches that compounds of interest are detected by *decreased* binding of antibodies that preferentially bind triggered structures or intermediates. The '427 patent, col. 10, lines 31-36. In contrast, present claim 4 recites that compounds of interest are detected by *increased* binding of antibodies that preferentially bind induced structures or intermediates. The '427 patent also teaches that compounds of interest are identified by *similar* binding of antibodies that recognize non-triggered states of the envelope protein. The '427 patent, col. 10, lines 37-43. In contrast, present claim 6 recites that compounds of interest are identified by *decreased* binding of antibodies that recognize non-triggered states of the envelope protein. The '427 patent contains no teaching or suggestion to detect compounds of interest in the manner recited in claims 4 and 6. Therefore, claims 4 and 6 are nonobvious over the '427 patent for this additional reason.

B. The Present Claims Are Nonobvious Over Jiang 1998 and Jiang 1999.

The Examiner stated that Jiang teaches that "any compound that induces conformational changes in HIV envelope proteins can be detected in the absence of cellular receptors." (Office Action, p. 5, ¶ 13.) Applicants respectfully disagree.

Jiang 1998 describes the characterization of monoclonal antibody NC-1, which was generated using peptide N36(L6)C34. Jiang 1998, abstract. This peptide folds into the fusogenic six-helix structure of gp41 that is induced after gp120 binding to the cellular receptor CD4. *Id.*, p. 10214, col. 2. Jiang 1998 shows that "NC-1 binds to the surfaces of HIV-1-infected cells *only in the presence of soluble CD4*." *Id.*, abstract (emphasis added). Jiang 1998 also states that NC-1 "will facilitate the characterization of the *receptor-induced* conformational changes in gp41." *Id.* at 10217 (emphasis added). Thus, Jiang 1998 does not teach or suggest that NC-1 can bind *membrane bound* viral envelope proteins or fragments thereof in the *absence* of cellular receptors or fragments thereof. In addition, Jiang 1998 does not teach or suggest a *screening method* for identifying compounds that selectively *induce* conformational changes in membrane bound viral envelope proteins or fragments thereof. Thus, the present claims are nonobvious over Jiang 1998.

Jiang 1999 teaches a method to screen for compounds that *inhibit* formation of the fusogenic six-helix bundle. Jiang 1999, e.g., abstract ("An . . . assay [] was developed using NC-1 . . . for screening of organic compounds for antiviral agents that may *interfere with* complex formation." (emphasis added)). Throughout Liang 1999, the compounds of interest are described as those that "inhibit," "block" or "interfere with" the formation of the gp41 core domain (i.e., six-helix bundle). *Id.*, p. 86, col. 2, lines 26 46; p. 93, col. 1, line 11 and col. 2, line 19; p. 94, col. 1, lines 27, 30, 34-35, 38, 44, and 46. In contrast, the present claims are directed to a screening method for identifying compounds that selectively *induce* conformational changes. Jiang 1999 contains no teaching or suggestion to screen for such compounds

Moreover, the assay in Jiang 1999 could *not* be used to identify compounds that selectively induce conformational changes. The assay in Jiang 1999

> *is based on the fact that the interaction of the N and C-peptides leads to the formation of a six-stranded fusion-active core domain* which can be specifically recognized by MAb NC-1. Therefore, any compounds that interact with the N or C-peptides and *interfere with* the formation of the six-helix complex may inhibit the HIV-1-mediated membrane fusion.

Id. at 93 (emphasis added) (citations omitted). Thus, the assay of Jiang 1999 is based on the *spontaneous formation* of the six-helix fusogenic bundle when synthetic N- and C- peptides are mixed, and the inhibition of this spontaneous formation by test compounds. The assay of Jiang 1999 could not be used to screen for inducers of those conformational changes, as in the presently claimed screening method, because these conformational changes occur spontaneously with the synthetic peptides of Jiang 1999. To modify Jiang 1999 as suggested by the Examiner would change its principle of operation. Therefore, the present claims are nonobvious over Jiang 1999. *See In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); *see* also MPEP § 2143.02(VI).

In contrast to Jiang 1999, in the present invention, the envelope protein or fragment thereof is *unable* to spontaneously change conformation. This is because the envelope protein or fragment thereof is "membrane bound" and has a conformation similar to the native, i.e., nonfusogenic, conformation. *See* Specification, page 16, ¶ 0055 ("For purposes of the invention, a viral envelope protein or glycoprotein can be in association with a lipid bilayer in a number of different ways, so long as the viral envelope protein or glycoprotein exists in one or more conformations similar to a conformation that the protein or glycoprotein exists in its native environment."); *see also* Jiang 1998, p. 10213, col. 2, lines 16-18 ("These conformational changes are thought to be involved in the transition from a native (nonfusogenic) to a fusion-active (fusogenic) state."). Moreover, Jiang 1999 does not teach or suggest that conformational changes could be induced in a membrane bound viral envelope protein or membrane bound fragment thereof in the absence of a cellular receptor or fragment thereof. Therefore, the present claims are nonobvious over Jiang 1999.

C. The Present Claims Are Nonobvious Over the Combination of References

The present invention is nonobvious over the '427 patent, Jiang 1998, and Jiang 1999, alone or in combination. The Examiner stated that it would have been obvious "to identify a compound that induces a conformational change[] of HIV envelope protein using either a membrane bound HIV envelope protein or N-and C-peptides" in the absence of a triggering agent like a cellular receptor. (Office Action, p. 5, ¶ 13.) Applicants respectfully disagree.

As discussed in detail above, Jiang 1998 describes the antibody NC-1, which binds the fusogenic six-helix bundle of gp41. Jiang 1999 and the '427 patent describe assays for identifying compounds that inhibit conformational changes in gp41 or other envelope proteins using NC-1 or other antibodies. In the case of the '427 patent, the assay comprises contacting a triggering agent and the envelope protein and testing the effect of a compound on the conformation of the envelope protein, while the Jiang 1999 assay involves contacting a compound with a first synthetic peptide and adding a second synthetic peptide to determine whether the compound inhibits the spontaneous formation of a six-helix bundle by the two peptides.

The combination of Jiang 1998, Jiang 1999 and the '427 patent does not teach or suggest an assay to identify compounds that selectively *induce* rather than inhibit conformational changes in a *membrane bound* envelope protein or *membrane bound* fragment in the *absence* of cellular receptors or fragments thereof. In fact, the combination of references does not even teach or suggest the *possibility* that compounds could selectively *induce* conformational changes in a *membrane bound* envelope protein or *membrane bound* fragment thereof, i.e., an envelope protein or fragment thereof with a conformation similar to the native (nonfusogenic) one. Therefore, the present claims are nonobvious over this combination of references.

The combination of references also does not teach or suggest that a compound should be identified based on (a) the *decreased* binding of an antibody or antibody fragment that preferentially binds to an epitope present on a structure or conformation that forms during viral entry, or (b) the *increased* binding of an antibody or antibody fragment that preferentially binds an epitope present only prior to induction. Therefore, claims 4 and 6 are nonobvious over the combination for this additional reason.

D. Conclusion

Therefore, the claimed invention is patentable in view of the '427 patent alone or in combination with Jiang (1998) and Jiang (1999). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

VII. Rejection For Obviousness Type Double Patenting

The Examiner maintained the rejection of claims 1-4, 6-9, 14, 18 and 20-25 over claims 1-19 of U.S. Patent No. 6,605,427 ("the '427 patent") under the doctrine of obviousness-type double patenting and extended the rejection to claims 26-33 in view of Jiang 1999. (Office Action, pp. 5-7, ¶¶ 14-18.) Applicants respectfully traverse the rejection.

The present claims are nonobvious over the claims of the '427 patent because the '427 patent claims are directed to a screening method in which *triggering agents* have the function of inducing conformational changes in viral envelope proteins, while that function is carried out by *candidate compounds* identified in the screening method of the present claims. As was discussed in detail in the Amendment and Reply filed October 26, 2006, all of the claims of the '427 patent are directed to a method of determining the effect of a compound on the ability of a viral envelope protein to form a conformational intermediate or an entry-relevant conformation, and require the use of a triggering agent (e.g., permissive cell or cellular receptor for a virus) to *induce conformational changes* in the envelope protein.

In contrast, the present claims all require the *absence* of cellular receptors or fragments thereof while *detecting induced conformational changes* to identify compounds of interest. Thus, the claimed invention omits an element (triggering agent) of the claims of the '427 patent while retaining the omitted element's function (inducing conformational changes). As explained in the MPEP, "the omission of an element and retention of its function is an indicia of nonobviousness." MPEP § 2144.04 II(B); *see* also *In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966).

In addition, the claims of the '427 patent *require* triggering agents such as cellular receptors or fragments thereof in order to identify compounds that inhibit the formation of fusion structures. Without triggering agents, inhibitors cannot be identified by the method of '427 patent. Thus, removing triggering agents would render the method claimed in the '427 patent unsatisfactory for its intended purpose. *See In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); and MPEP § 2143.01(V).

The pending claims are therefore nonobvious over the claims of the '427 patent. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

V. Rejection Under 35 U.S.C. § 112, First Paragraph: New Matter

The Examiner rejected claims 32 and 33 because the phrase "wherein said cellular receptors or fragments thereof do not induce said conformational change" is allegedly new matter. (Office Action, p. 7, ¶¶ 21-22.) Applicants respectfully traverse the rejection.

Applicants note that the quoted phrase is not found in claim 32. Therefore, the rejection of claim 32 on this ground appears to be in error.

Moreover, the specification fully supports claim 33, in that it clearly contemplates that once a viral envelope protein has been selectively induced in the absence of a cellular receptor, the induced envelope protein would no longer be fusogenic under normal circumstances, e.g., when contacted with a cellular receptor or fragment thereof. The specification supports this idea in a number of passages. For example, the specification states, "[i]n the present invention small molecule inhibitors of viral entry are identified by their ability to interact with either gp120 or gp41 in the absence of cellular receptors resulting in the formation of the six-helix bundle structure in gp41 and *inactivating* virus." Specification, at p. 8, ¶ 0008 (emphasis added). The specification also states,"[t]he present invention provides methods of screening for compounds that induce conformational changes in viral envelope proteins that result in *loss of function by envelope structures necessary for virus entry into permissive cells*." Specification, at p. 10, ¶ 0033 (emphasis added). It also states:

> the present invention is directed to a screening assay for inhibitory compounds which involves determining the ability of a candidate compound to induce conformational changes in viral envelope protein or glycoprotein or fragments thereof, such that the conformational changes render the cell, virion, pseudovirion, membrane vesicle, lipid bilayer or liposome

> expressing or bearing envelope protein or glycoprotein *no longer fusogenic*.

Specification, at page 11, paragraph 0034 (emphasis added). In addition, the specification states:

> [t]he changes in conformation render a cell, virion, pseudovirion, membrane vesicle, lipid bilayer or liposome expressing or bearing envelope protein, glycoprotein or fragments thereof, *no longer fusogenic* by the induction of such conformational structures and intermediates away from a permissive cell. . . . *This renders the virus incapable of fusion when proximal to a permissive cell.*

Id., page 17, paragraph 0061 (emphasis added). Also see page 17, paragraphs 0059-0060 (defining and exemplifying "permissive cell"). Therefore, the specification inherently, if not explicitly, supports the phrase "wherein said cellular receptors or fragments thereof do not induce said conformational change" in claim 33.

Based on the passages quoted above, an artisan of ordinary skill would have recognized that Applicants had possession of the invention presently recited in claim 33. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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